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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/037,110	10/22/2001	Patrizia Caldirola	13425-052001 / 00382-US	5944

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EXAMINER
MCKENZIE, THOMAS C

ART UNIT	PAPER NUMBER
1624	10

DATE MAILED: 04/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/037,110	CALDIROLA ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25 and 27-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *32* is/are allowed.

6)☒ Claim(s) *1-7,9,11-15,18,20,22-25,27-31,33-41 and 44-47* is/are rejected.

7)☒ Claim(s) *8,10,16,17,19,21,42 and 43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is in response to amendments filed on 2/10/03. Applicants amended claims 1, 2, 12-18, 22, 24, and 25. Applicants canceled claim 26. Claims 28-47 are new. There are forty-six claims pending and forty-six under consideration. Claims 1-21, 28-43, and 47 are compound claims. Claim 22, 23, and 46 are composition claims. Claims 24, 25, 27, 44, and 45 are use claims. This is the second action on the merits. Claims 18 and 23 were previously allowed. Objection was previously made to claims 10 and 19-21. All other pending claims had been rejected. This action Is made non-Final because new art and enablement rejections are being applied. The indicated allowability of claims 18 and 23 is withdrawn because of the newly applied art. The application concerns some 1-sulfonylindole compounds, compositions, and uses thereof.

Priority

2. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(a)-(d) based upon an application filed in Sweden on 10/20/00. Applicants pointed out that 10/20/01 was a Saturday. Thus, a claim for priority under 35 U.S.C. 119(a)-(d) can be based on said application.

3. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(a) as follows: the later-filed application must be an application for a patent for an invention which is also

disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994). The Swedish application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-18 and 20-47 of this application. The present claims are to molecules with 12 different heterocyclic radicals attached either to position 4, position 5, or both positions of an indole core. Swedish Application 0003810-9 discloses indole compounds with only nine different heterocyclic radicals attached only to position 4 of an indole core. A benzyl group is a presently claimed substituent on these heterocyclic radicals. In the Swedish parent it is not. The species of the present claim 19 is also named in the Swedish parent application.

4. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 1-18 and 20-47 of this application. The contents of this provisional application appear identical to those of Swedish Application 0003810-9 discussed above.

5. Thus, claims 1-18 and 20-47 have an effective filing date of 10/22/01. Claim 19 has an effective filing date of 10/20/00.

Response to Amendment

6. Applicants' deletion of "prophylaxis" overcomes the enablement rejection made in point #5 of the previous office action. Applicants amendments, requiring either R^4 or R^5 to be a non-hydrogen atom overcome the art rejections over Illi (Synthesis), Nyasse (Journal of Organic Chemistry), Goulaouic-Dubois (Journal of Organic Chemistry), and Artico (WO 96/33171 A1) made in points #6-#9. All these references require both positions to be unsubstituted.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 24 and 25 remain rejected and claims 34, 35, 44 and 45 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "a disease mediated by the serotonin-related 5-HT_6 receptor" is indefinite. What are these disorders? In line 27, page 1 and in lines 20-22, page 2 Applicants list some specific diseases they intend to treat. However, these passages use open language and do not specifically identify which diseases fall into this category. The phrase "a CNS disorder" is indefinite because

all this does is provide the location of the disease. Lines 20-21, page 3 list schizophrenia, Parkinson's, and depressions as CNS disorders. Are these all? Is ADHD or drug abuse such a disorder? How about brain cancer, ALS, or bipolar disorder? The Examiner suggests listing the diseases that Applicants' intend to treat in the claims being mindful of enablement requirements.

Applicants make three arguments that Applicants' terms define themselves, that Maddaford ('893) and Robichaud (Ann. Reports Med. Chem.) among other use and define the first phrase, and that Maddaford ('893) and Williams (Ann. Reports Med. Chem.) define and use the second. This is not persuasive. Firstly, a circular definition is not a proper definition. In the previous action, the Examiner asked if some specific diseases were covered by Applicants claim language. If Applicants cannot answer, how is the public to understand the scope of the claim?

Secondly, the references cited do not agree among themselves as to which diseases are meant and disagree with Applicants. Applicants list memory disorders, schizophrenia, Parkinson's, depression, ADHD, and drug abuse among such disorders. Maddaford ('893) does not list ADHD, and drug abuse but does add manic depression, neurological disturbances, ALS, Alzheimer's disease, and Huntington's disease but Applicants do not. Briggs (US 2003/0045527 A1) does not list memory disorders, ADHD, and drug abuse among such disorders but does

add irritable bowel syndrome and obesity. Neither Applicants nor Maddaford ('893) list these. With such contradictions it is clear there is no art-recognized list of such diseases. The table to which Applicants point in Williams (Ann. Reports Med. Chem.) does not, in fact, purport to list all CNS disease but rather a few where there is current experimental work. In the final paragraph on page 2, even the reviewer admits that the DSM-IV is incomplete. In any event, do Applicants intend to use their compounds to treat spinal cord injury, sexual disorders, stroke, and pain? These are listed by Williams (Ann. Reports Med. Chem.) as CNS diseases.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24, 25, 27, 44, and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating depression and psychosis, does not reasonably provide enablement for treating every "CNS disorder" or every "disease mediated by the serotonin-related 5-HT_6 receptor". The specification does not enable any physician skilled in the art of medicine, to use the invention commensurate in scope with these claims. "The factors to be considered [in making an enablement rejection] have been summarized as the

quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Determining if any particular claimed compound would treat every CNS disease or every "disease mediated by the serotonin-related 5-HT_6 receptor" would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases which occur in the brain and spinal column, a large degree of experimentation. b) The direction concerning treating such diseases is found in the lines 20-22 on page 2, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 11, page 10 to line 17, page 11. Applicants describe doses in lines 18-26, page 11 and propose a 50,000-fold range of doses. Since, as discussed below, no pure "serotonin-related 5-HT_6 receptor" agent has ever been used to treat any human disease, how is the skilled physician to know what dose to use? Applicants provide no dosing schedules required to practice their invention. There is a single *in vitro* binding assay described in lines 1-20, page 61 with no data. It is unclear if this assay is

related to all CNS diseases. It is also unclear if the Applicants' compounds are agonists or antagonists at "the serotonin-related 5-HT_6 receptor". There is a single obesity related disease model in the mouse described in the passage spanning line21, page 61 to line 10, page 63. Again there is no0 data presented. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease, which involves physiological activity. e) The state of the clinical arts in "disease mediated by the serotonin-related 5-HT_6 receptor" is found in the review of Robichaud (Ann. Reports Med. Chem.). he reports in the final sentence on page 16 that several nonselective agents bind to this receptor. The final part of the preceeding sentence makes clear that in 2000, experimental work was under way to determine if selective binding agents were useful therapeutically but as of that date none were understtod to be so.

f) The artisan using Applicants invention would be a physician with a MD degree, board certified in psychiatry and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

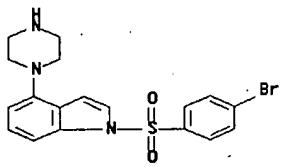
h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term CNS disease. Thus, undue experimentation will be required to practice Applicants' therapeutic claims.

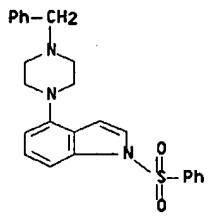
Claim Rejections - 35 USC § 102

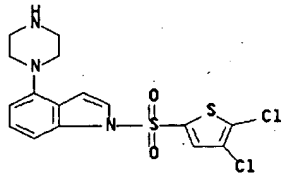
9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 6, 7, 9, 11-13, 15, 18, 22-25, 27-31, 33-41, and 44-47 are rejected under 35 U.S.C. 102(e) as being anticipated by Kelly (US 2002/0115670 A1, Ref AB). This reference claims priority to provisional application 60/245,118, which appears identical in content to the reference. A copy of provisional application 60/245,118 is provided for Applicants' convenience. Thus, the reference has an effective filing date of 11/2/00. The compounds shown below fit formula (I) with





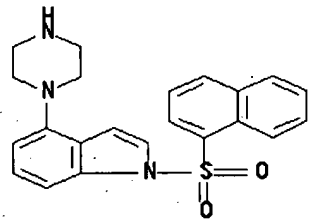


$R^2 = R^3 = R^5$ = hydrogen, Ar = substituted phenyl or substituted thienyl, and R^4 = 1-piperazinyl with R^6 = hydrogen or benzyl. They have Registry Number 412048-92-1, 423174-17-8, and 423175-41-1. They are found in paragraphs [0049], [0054], and [0051] respectively on page 3 of the reference. See also Table I, page 6, Ex. 36, page 9, Ex 76, Ex 83, Ex 86, Ex 95, Ex 97, Ex 100, page 13, and claims 1-17.

Ex 76, Ex 83, Ex 86, Ex 95, Ex 97, and Ex 100 of the reference have the piperazine ring attached to position 5. Thus, Applicants' claims 28, 30, 31, 33-41, 45, and 47 are anticipated.

10. Claims 1-5, 11-14, 18, 22-25, 27, 29, 37, 44, and 46 are rejected under 35 U.S.C. 102(e) as being anticipated by Briggs (US 2003/0045527 A1). This reference claims priority to provisional application 60/298,834, which provides support for the naphthalene and phenyl sulfonamides, as well as for three specific

compounds. A copy of provisional application 60/298,834 is provided for Applicants' convenience. Thus, the reference has an effective filing date of 6/15/01. The compound shown below fit formula (I) with $R^2 = R^3 = R^5 =$ hydrogen, Ar = 1-naphthalenyl, and R^4 = 1-piperazinyl with R^6 = hydrogen. It has



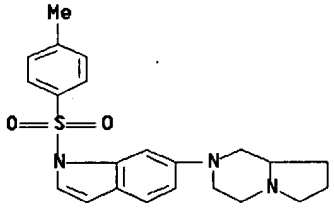
Registry Number 412048-52-3 and is found in paragraph [0060], page 4 of the reference. It is also found pictured in line 19, page 20 of the provisional Application. See also the compounds of paragraphs [0061] and [0066] of the reference. They may also be found pictured in line 11, page 21 and line 14, page 24 of the provisional application. See also claims 1-15 of the reference.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 11, 13, 14, 22, 24, 27, 29, 36, 37, 44, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD). The reference teaches the compound with registry number 299433-11-7 shown below. The Applicant claims the compounds with a



hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical attached at position 4 of the indole core. The reference teaches a compound with hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical attached at position 6 of the indole core. The compound shown in the reference in Figure 1, page 1720 and is compound **4b**. A second relevant compound is **4a**. The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 4 and the reference teaches attachment at position 6. These are *per se* obvious ring position isomers and require no specific teaching.

Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) appeared in the 15 issue of Volume 10. A photocopy of the cover page of this issue is provided for Applicants convenience. Issue No. 15 has a publication date of 7 August 2000 and, in fact, was received by the USPTO library on Aug 1, 2000.

In the last sentence, first paragraph, second column, page 1720 Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) teaches that "specific concentrations of test compounds" were prepared. These presumably were in water, saline , or buffer and are compositions. Thus, Applicants claims 22 and 46 are made obvious. Binding data for the 5-HT_6 receptor are presented in Table 1, page 1720. Selectivity for the 5-HT_6 receptor for compound **4a** is presented in Table 2, page 1720. The expectation that compound **4a** is useful for treating schizophrenia, depression, and memory dysfunction is taught in the final paragraph on page 1721. Thus, Applicants' claims 24, 27, 44, and 46 are made obvious.

Applicants should be aware that determination of absolute binding affinities to receptors is capricious and that proper comparison of such affinities among different groups of compounds is best done on a side-by-side basis with suitable positive and negative controls.

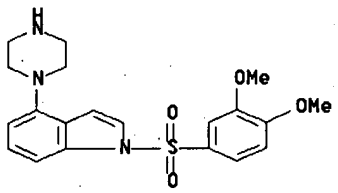
The synthesis taught by Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD) is a coupling reaction, similar to that used by Applicants. Synthesis of the ring position isomers of the compounds of this reference requires only use of a ring position isomeric bromo indole. Thus, the reference is an enabling disclosure for the synthesis of Applicants' claimed compounds.

12. Claims 28, 30, 33-40, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isaac (Bioorganic & Medicinal Chemistry Letters, ref ADD). The teachings of the reference are discussed above. The Applicants claim the compounds with a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl radical attached at position 5 of the indole core. The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 5 and the reference teaches attachment at position 6. These are *per se* obvious ring position isomers and require no specific teaching.

13. Claims 5, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (US 2002/0115670 A1, Ref AB). The reference teaches the compound of Ex 95, page 13. The Applicant claims the compounds with a 2-naphthyl radical as Ar and a piperazine radical as R_4. The reference teaches a compound with a 2-naphthyl radical as Ar and a piperazine radical as R_5. The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 4 and the reference teaches attachment at position 5. These are *per se* obvious ring position isomers and require no specific teaching.

14. Claims 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kelly (US 2002/0115670 A1, Ref AB). The reference teaches the compound

with registry number 412048-59-0 shown below. The Applicant claims the compounds with methoxy groups in the 2 and 5 positions. The reference teaches a compound with methoxy groups in the 3 and 4 positions. The compound shown in the reference in paragraph [0047], page 3, Ex 4, page 6, and Ex No. 4, page 14. The difference between the claimed and taught compounds is the point of attachment of the methoxy substituents. Applicants claim attachment at positions 2 and 5 and the reference teaches attachment at positions 3 and 4. These are *per se* obvious ring position isomers and require no specific teaching.



15. Claims 28, 30, 31, 33-40, 45, and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briggs (US 2003/0045527 A1). The teachings of the reference are discussed above. The Applicants claim the compounds with a piperazine radical attached at position 5 of the indole core. The difference between the claimed and taught compounds is the point of attachment of the heterocyclic radical. Applicants claim attachment at position 5 and the reference teaches attachment at position 4. These are *per se* obvious ring position isomers and require no specific teaching.

Allowable Subject Matter

16. Claim 32 is allowed. Claim 19 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants' effective priority date makes this claim allowable over the art cited above. Claims 8, 10, 16, 17, 21, 42, and 43 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicants' pyridyl and benzylsulfonyl compounds are novel over the art cited above.

Conclusion

17. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (703) 308-9806. The FAX number for before final amendments is (703) 872-9306. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, you can reach the Examiner's supervisor, Mukund Shah at (703) 308-4716. Please direct general inquiries or any inquiry relating to the status of this application to the receptionist whose telephone number is (703) 308-1235.

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
April 23, 2003

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PRIMARY EXAMINER
GROUP - ART UNIT 1624